Combined Treatment of Progressive Encephalitis in an X-linked Agammaglobulinemia Patient

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ABSTRACT

Most patients with X-linked agammaglobulinemia are susceptible to infections, while some cases also suffer from inflammatory or autoimmune complications. We describe a patient with progressive encephalitis who improved after the use of immunomodulatory treatment with corticosteroids, fluoxetine, and nitazoxanide. In most of the cases the evolution of the progressive encephalitis is complicated and catastrophic. Based on our experience and the review of the literature, we propose the use of this combined treatment to control this devastating complication.

Keywords: Agammaglobulinemia; Immunomodulators; Primary immunodeficiency diseases; Neuroinflammatory diseases; Therapy

INTRODUCTION

X-linked agammaglobulinemia (XLA) is characterized by a low number of B cells, agammaglobulinemia, and increased susceptibility to infections by encapsulated bacteria and certain bloodborne viruses. Patients with XLA are generally considered to have a low risk of autoimmune or inflammatory disease compared to other errors of innate immunity cohorts. However, data from a national registry indicated that a significant proportion of patients with XLA have symptoms consistent with the diagnosis of an inflammatory condition. A number of patients with XLA have been reported to have progressive encephalitis of uncertain etiology. We present a patient with XLA who developed progressive encephalitis and showed improvement with a combined treatment with fluoxetine, nitazoxanide, and corticosteroids.

CASE PRESENTATION

A 14-year-old boy was diagnosed at 4 years of age with XLA (hypogammaglobulinemia, no CD19 cells, no expression of Bruton Tyrosine Kinase (BTK) by Western Blot), and monthly intravenous immunoglobulin (IVIG) at 800 mg/kg/dose was started. At 4 years old, he had his first episode of seizures, and at 10 years old, he was diagnosed with focal epilepsy and treated with magnesium valproate. During his initial neurological evaluation, he was diagnosed with a mild intellectual disability. In December 2018, at the...
age of 12, he had an increase in the frequency of seizures, and was subsequently switched to oxcarbazepine. He developed progressive neurological deterioration characterized by the loss of cognitive abilities such as dyscalculia, anomic dysphasia, and a decline in language skills. He also had dysgraphia and tremors. The patient had problems with social interaction and irritability, and stopped attending school. A mini-mental state examination (MMSE) revealed a score of 3 points (normal > 24 points).

Magnetic resonance imaging (MRI) of the brain revealed extensive multifocal changes in the white matter, characterized by a hyperintense signal in T2 in the frontoparietal and temporal regions. Additionally, cortical and subcortical atrophies were observed. The cerebral spinal fluid (CSF) showed 5 cells/mL and a protein concentration of 24 mg/dL. Microbial cultures and specific polymerase chain reaction (PCR) for viruses (including JC and BK viruses) and bacteria were negative.

In July 2019, a brain biopsy was performed. During the surgical procedure, a dose of dexamethasone (0.15 mg/kg every 6 hours) was administered, after which he had an improvement in neurological status with the disappearance of tremors and started to talk coherently. A brain biopsy revealed chronic perivascular lymphocytic infiltration without intracytoplasmic inclusions. No special stains or PCRs were performed. He received anti-inflammatory therapy with prednisone (10 mg/day) because of the lymphocytic infiltration, and he also began taking fluoxetine (20 mg/day) and nitazoxanide (500 mg/day), which have been reported to have antiviral effects in the literature. The patient had clinical improvement in neurological symptoms, and a follow-up MRI 10 months later showed similar findings of atrophy and leukoencephalopathy compared with the initial MRI. At the last neurological evaluation, there was an objective improvement in higher brain functions such as memory, attention, calculation, speech, and language, with a recent MMSE of 8. The patient is still on low-dose prednisone, fluoxetine, and nitazoxanide and continues to remain stable.

**DISCUSSION**

XLA patients can present with viral chronic meningoencephalitis as well as progressive multifocal leukoencephalopathy. There are a few cases in the literature of XLA patients presenting with progressive encephalitis of uncertain etiology. All of them had a negative infectious disease assessment, had neurological deterioration after IVIG treatment, brain biopsies demonstrated lymphocytic infiltration, and most of them had a fatal outcome (Table 1).

Gall et al. reported a 29-year-old male with XLA and progressive neurodegenerative disease without an identifiable infectious etiology who was treated with IVIG and interferon-alpha without improvement. In other patients, intrathecal immunoglobulin and pleconaril have been used without evidence of benefit. In all these patients that present with chronic encephalitis of uncertain etiology, it has been speculated that this may result from an autoimmune reaction against brain tissue, an undefined infectious agent, or a complication of intravenous immunoglobulin therapy.

Frequently, it is challenging to distinguish between infectious diseases and this progressive encephalitis of uncertain origin when considering clinical, laboratory, imaging, and histopathological aspects. Recently, in patients with XLA suffering from unidentified progressive encephalitis, new diagnostic tests allowed the identification of new viruses as the possible etiology of the neurological disease. Fremond et al. reported a 10-year-old boy who presented with progressive encephalitis, and only after next-generation sequencing (NGS) of the brain biopsy specimen was an astrovirus documented. He responded to a combined treatment of steroids, interferon-alpha, and ribavirin.

Wilson et al. reported an XLA patient with Cache Valley Virus, a mosquito-borne orthobunyavirus detected by NGS of the CSF and brain tissue, as the cause of fatal progressive encephalitis. Although an infectious etiology was not identified in our case, we cannot rule out a viral etiology that causes the inflammatory process of the CNS. High-dose corticosteroids have been recommended in viral encephalitis to improve disturbances of consciousness. Of note, in the cases of XLA, complicated with non-infectious chronic encephalitis, corticosteroids were avoided due to concerns of exacerbating an underlying infection (Table 1). Importantly, our patient has not had an infectious complication since corticosteroid treatment was started. We believe that corticosteroids could be beneficial as an add-on treatment to stabilize progressive encephalitis in XLA.
## Treatment of Progressive Encephalitis in XLA

Table 1. Comparative features of previously reported XLA patients with non-infectious encephalitis and our case.

<table>
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<tbody>
<tr>
<td>Age at presentation</td>
<td>6 years</td>
<td>4 years</td>
<td>14 years</td>
<td>20 years</td>
<td>19 years</td>
<td>20 year</td>
<td>6 years</td>
<td>15 months</td>
<td>2 years</td>
<td>13 years</td>
</tr>
<tr>
<td>Origin</td>
<td>NR</td>
<td>Russia</td>
<td>Iran</td>
<td>Turkey</td>
<td>Philippines</td>
<td>USA</td>
<td>Japan</td>
<td>Japan</td>
<td>India</td>
<td>Mexico</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>Difficulty walking, weakness, difficulty swallowing, mental and motor capabilities fade</td>
<td>Difficulty walking, deterioration of speech</td>
<td>Headache, irritability, regression in language skills, weakness in lower extremities</td>
<td>Progressive cognitive decline, involuntary movements, gait disturbance</td>
<td>Hearing impairment at 2 years of age, dystonia and progressive neurodegeneration at 19 years of age</td>
<td>Tremor, anhedonia, poor memory, ataxia</td>
<td>Hearing disturbance progressive intellectual disability at 9 years of age</td>
<td>Seizures, hemiparesis, progressive lethargy</td>
<td>Progressive cognitive decline, seizures, dyscalculia, the ability to oral expression, regression in language skills, anosmia, dysgraphia</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>NR</td>
<td>Negative</td>
<td>Normal</td>
<td>Negative</td>
<td>Normal</td>
<td>NR</td>
<td>Pleocytosis, 67 cells/µL, 78% mononuclear CD4+ and CD8+ T cells</td>
<td>Elevated protein</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Image</td>
<td>NR</td>
<td>MRI: diffuse cerebral atrophy, focal lesions with high signal intensity on T2w and FLAIR in periventricular and subcortical regions</td>
<td>MRI: brain atrophy</td>
<td>MRI: cerebral and cerebellar atrophy, hyperintensities in the mesial temporal regions</td>
<td>MRI: atrophy of the caudate nuclei</td>
<td>MRI: severe global atrophy</td>
<td>CT: cerebral atrophy</td>
<td>MRI: inflammatory changes in the basal ganglia, hypothalamus, midbrain, and pons, multiple nodular lesions</td>
<td>MRI: frontal subcortical white matter lesions</td>
<td>MRI: cortical and subcortical atrophy, hyperintensities in T2w, and FLAIR in frontal and temporal regions.</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Biopsy</th>
<th>NR</th>
<th>Massive perivascular CD8+ lymphocyte infiltration in the cerebral cortex and leptomeninges</th>
<th>NR</th>
<th>NR</th>
<th>NR</th>
<th>Diffuse neuronal loss and gliosis in the cerebral cortex, perivascular infiltration of lymphocytes and macrophages in leptomeninges and brain parenchyma</th>
<th>NR</th>
<th>Autopsy: perivascular CD3+ lymphocyte infiltration, microglial proliferation with nodule formation</th>
<th>Perivascular lymphocyte infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Interferon-alpha-2B, IVIG</td>
<td>NR</td>
<td>Intraventricular immunoglobulins</td>
<td>Acyclovir, high-dose IVIG</td>
</tr>
<tr>
<td>Outcome</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Lost to follow-up</td>
<td>Alive at follow-up</td>
<td>Alive at follow-up</td>
<td>Deceased</td>
<td>Deceased</td>
<td>Deceased</td>
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Fluoxetine and nitazoxanide were added due to their reported antiviral properties.\textsuperscript{13-17} Nitazoxanide inhibits the replication of a broad range of RNA and DNA viruses, including astrovirus and Japanese encephalitis virus.\textsuperscript{16,17} Nitazoxanide and its active circulating metabolite, tizoxanide are active in vitro against a broad range of anaerobic gram-positive and gram-negative bacteria, as well as certain \textit{Mycobacterium tuberculosis} strains.\textsuperscript{17} Fluoxetine, an antidepressant drug that acts as a selective serotonin reuptake inhibitor, reduces the synthesis of enteroviral RNA and has been used in chronic enterovirus encephalitis.\textsuperscript{13,15}

Chetty et al. report an 8-month-old patient with SCID (severe combined immunodeficiency) and enterovirus encephalitis who was treated successfully with a combination of favipiravir, fluoxetine, and IVIG.\textsuperscript{14} Goftsgteyn et al, reported that fluoxetine, IVIG, and corticosteroids halted the progression of enteroviral encephalitis in an XLA patient.\textsuperscript{13} The diagnosis of enterovirus encephalitis was made through direct tissue real-time PCR testing for enterovirus RNA.\textsuperscript{13} Electron microscopy in search of virus particles and PCR or NGS techniques should be considered in all patients with chronic progressive encephalitis in XLA when routine infectious tests are negative.

XLA has symptoms consistent with the diagnosis of an inflammatory disease, including inflammatory bowel disease, arthritis, enthesitis, membranoproliferative glomerulonephritis, Kawasaki disease, and hemophagocytic lymphohistiocytosis.\textsuperscript{18-23} Inflammatory conditions associated with an infectious trigger (echovirus dermatomyositis-like disease and pyoderma gangrenosum due to Helicobacter species) have also been described.\textsuperscript{12,23}

Diverse mechanisms may underlie these manifestations; XLA patients present a dysregulated TLR (Toll-like receptors) signaling in the absence of BTK. BTK has been found to function as a physiologic inhibitor of NLRP3 (NLR Family Pyrin Domain Containing 3), favoring inflammasome activation.\textsuperscript{24,25} Ray et al. reported a patient with Good’s syndrome presenting with a combination of autoimmune and viral encephalitis.\textsuperscript{26} In XLA, in the absence of a positive autoantibody serology, autoimmune encephalitis can’t be entirely excluded. Neuropathological features of autoimmune encephalitis overlap with that of viral encephalitis.\textsuperscript{26} In both documented infectious progressive encephalitis and undetermined progressive encephalitis, CD4\textsuperscript{+} and CD8\textsuperscript{+} lymphocytic infiltration are observed. In the case that we present, the decision to continue corticosteroids was made based on the presence of central nervous system inflammatory reaction with lymphocytic infiltration on brain biopsies and previous reports in both infectious and unidentified etiology progressive encephalitis of the presence of elevated proinflammatory cytokines in CSF.\textsuperscript{2,13}

In conclusion, we propose that in progressive encephalitis of uncertain etiology in XLA, the combination of fluoxetine, nitazoxanide, and corticosteroids could stabilize the disease.

**STATEMENT OF ETHICS**

The parents have provided informed consent for the publication of the case. Since this is a single case report, ethics approval was not required.

**FUNDING**

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**CONFLICT OF INTEREST**

Dr. M.A.Y.N has received lecture fees from Shire, CSL Behring, and Octapharma. The rest of the authors declare no conflict of interest.

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**REFERENCES**


